

This issue of Bandolier may look a little different. The reason for that is that after 10 years of setting it on a programme called PageMaker, we have moved to the latest system called InDesign. As with many enormously complex programmes we only use a fraction of its capability. The problem is knowing what parts and where to find them. And then there is the blind trust that they will work, and the confusion and disappointment when the one thing one wants to work doesn't.

Pause for thought

Evidence can be the same. We can go on happily doing something for years and be brought up short by evidence that makes us wonder. This month Bandolier spends a bit of time looking at the evidence around paracetamol (acetaminophen for US readers) in osteoarthritis. Two systematic reviews and several recently-published RCTs question whether there is any difference between paracetamol and placebo. Larger, longer, and better trials consistently say no.

We need to stop and think here. We know that paracetamol is an analgesic in acute pain, and in some shorter but smaller and less good studies in osteoarthritis. Is this a paracetamol problem, or a trial sensitivity problem? Either way it suggests we put on our thinking caps.

Keeping taking the medicine

Bandolier continues to be intrigued by the large proportion of patients who do not take prescribed medicines. This issue of compliance has large repercussions, for individual patients and for health services. There are big costs involved. And we know that compliance is not the 'in' word, and that using compliance, concordance, or adherence as synonyms will get us into trouble with someone. Whatever, evidence and insight are more important than labels here.

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PARACETAMOL FOR OSTEOARTHRITIS

I have made a heap of all that I could find.

So said Nennius when writing his *Historia Brittanorum* in the ninth century. He was something of an indiscriminate historian, but the words have resonance for us when trying to answer what should be a relatively simple question: how good is paracetamol for treating OA?

We have two recent systematic reviews [1,2]. One looks at trials comparing paracetamol to NSAIDs and placebo, while the other looks at comparisons with NSAIDs alone.

Both share the same problem. There are not that many trials. Do we make a heap of them, or try to select those most likely to inform? The problem is confounded because since they were done, newer trials have been published which the reviews did not include.

So given that this is a question we would like to be answered, it makes a useful exemplar for applying some rules that Nennius might have applied – those of quality, validity, and size. Let's start by looking at the reviews individually, and then move on to an update with the new trials.

Zhang et al [1]

This review chose RCTs of paracetamol versus placebo and/or NSAIDs (which for our purposes loosely means traditional NSAIDs like diclofenac and newer cox-2 selective inhibitors like rofecoxib and celecoxib) published to July 2003. Only studies in osteoarthritis with radiographic or clinical diagnosis, or of pain associated with osteoarthritis were used. Trials had to be randomised.

There were no limits on dose of paracetamol, or of duration of trial, and both abstracts and full publications were accepted.

They found 10 trials, two of which were abstracts. There were four comparisons with placebo and eight with NSAIDs. The dose of paracetamol was 2,600 mg to 4,000 mg daily, and trial duration was one week to two years, but mostly of six weeks or less. A number of the trials were quite small.

The headline results were these: paracetamol was barely different from placebo, and was less effective than NSAIDs. Adverse events were no different for paracetamol or placebo, while NSAIDs caused more GI discomfort.

Wegman et al [2]

A different strategy was used, seeking only trials comparing paracetamol and NSAID to end 2001. Again osteoarthritis was the target condition, with pain and disability outcomes reported in full publications. It also reviewed guidelines.

This review had five trials with doses of paracetamol between 990 and 6,000 mg daily. These had a duration that went from a single dose, to two years. Three of the trials appeared in the Zhang review [1]. The headline result was a small benefit in pain relief in favour of NSAIDs.

How many trials are there?

A Bandolier search identified 16 trials that examined paracetamol in osteoarthritis and were randomised (not including abstracts). Which of these 16 trials do we want to include in a review? If we accept any size of trial, but specify a minimum quality criterion of being randomised and double blind, then that still leaves us with 16 trials. But five of the 16 trials had fewer than 50 patients and seven had fewer than 100.

What about validity? Should we accept any dose, for instance? That doesn't make much sense, so we will accept only trials with a paracetamol dose of 3,000 or 4,000 mg a day, doses generally used in OA treatment. We can remove three trials, with 990 mg, 2,000 mg, and 6,000 mg.

Should we accept any duration? A single dose trial seems daft, so there should be some minimum. Six to 12 weeks tends now to be the minimum in osteoarthritis trials, so we will accept trials that last at least four weeks, to be generous. There is one single dose trial, four of one week, three of two weeks and one of three weeks.

TABLE 1: Discontinuations and adverse events in trials comparing paracetamol with placebo and NSAIDs (traditional and coxibs)

Outcome	Comparator	Number of		Outcome (%) with		Relative risk (95% CI)	NNH/NNTp (95% CI)
		Trials	Patients	Paracetamol	Comparator		
Discontinuations							
All-cause	Placebo	2	836	26	30	0.9 (0.7 to 1.1)	
	NSAID	5	1211	32	22	1.4 (1.2 to 1.6)	10 (6 to 20)
Lack of efficacy	Placebo	2	836	14	18	0.8 (0.6 to 1.1)	
	NSAID	4	1137	13	7	2.1 (1.5 to 3.1)	15 (10 to 33)
Adverse event	Placebo	no data					
	NSAID	4	1137	9	12	0.6 (0.4 to 0.9)	31 (15 to >100)
Adverse events							
Any	Placebo	2	1972	25	24	1.0 (0.9 to 1.2)	
	NSAID	4	2333	34	38	1.0 (0.9 to 1.1)	
Gastrointestinal	Placebo	2	1972	10	9	1.1 (0.9 to 1.5)	
	NSAID	4	2333	14	16	0.9 (0.7 to 1.1)	
Serious	Placebo	2	1972	0.9	0.9	1.0 (0.4 to 2.6)	
	NSAID	2	1767	0.6	0.9	0.7 (0.2 to 2.0)	

Bold indicates NNH; bold, shaded indicates number needed to treat to prevent one event (NNTp)

Another outburst of generosity to equate 2,600 mg daily as close to 3,000 mg leaves us with seven trials, three with comparisons with placebo, and six with comparisons with NSAIDs or coxibs. The nine we have omitted were all of short duration, and predominantly tiny.

What we have left are trials we think we ought to be able to trust to give sensible and meaningful results. Both reviews found the trials published to the time of their search, 5 [1], and 3 [2] respectively. Two more trials were published in 2004. Details of individual trials included and excluded will be available on the Internet.

Paracetamol versus placebo

No simple pooling of results is possible for efficacy in the three reports (2,000 patients) comparing paracetamol 4,000 mg daily with placebo over 6-12 weeks. One report had four trials, and only one of those four trials showed any hint of difference between paracetamol and placebo.

The largest and best trial [3] used a series of cut points, none of which showed a difference. It did suggest that there might be a benefit of paracetamol over placebo in a subgroup of patients who had no sudden increase in pain, and without night pain, but this was a small proportion of the whole. There were no differences in discontinuations overall or because of lack of efficacy, or in adverse events (Table 1).

Paracetamol v NSAIDs and coxibs

Again, simple pooling of efficacy results was not possible in the six reports (2,100 patients) that reported them. Paracetamol doses were 4,000 mg daily in five trials and 2,600 mg in one. One report had two trials, and in seven trials overall five found a significant benefit for NSAID over paracetamol for at least one efficacy measure.

Paracetamol had more discontinuations both overall and because of lack of efficacy. Over 6-12 weeks, compared with NSAIDs, one more patient would discontinue overall for every 10 patients treated with paracetamol, and one more would discontinue for lack of efficacy for every 15 patients treated. Paracetamol was associated with fewer patients discontinuing because of adverse events, with one fewer patient discontinuing because of adverse events for every 31 treated (though with very wide confidence intervals, Table 1). There were no differences between paracetamol and NSAIDs for patients reporting any adverse event, or for gastrointestinal adverse events or serious adverse events (Table 1).

Comment

It is interesting to ask where this takes us. We know that paracetamol is an analgesic, and experience is that in osteoarthritis it works for some people. Because it is safe, guidelines that make it their first line treatment option remain sensible.

We know that NSAIDs and coxibs are more effective than paracetamol. More patients with osteoarthritis will have a good effect, but more of them will have some adverse event that will make them want to stop taking it.

Overall, in six to 12 weeks after starting on paracetamol or NSAIDs something like 30% of people will stop taking their medicine for one reason or another. About one in three or four will have some adverse event, even with placebo, about one in 10 will have a gastrointestinal adverse event, even with placebo, and one in a 100 or so will have a serious adverse event, even with placebo.

Pulling these trials together is not an exercise in intellectual nihilism. We have deliberately chosen the best trials, in terms of their quality, their validity, and their size. Yet we are disappointed at their ability to discriminate between paracetamol, a known analgesic, and placebo, and between NSAIDs and paracetamol, when we know NSAIDs are likely to be better. It would be difficult, though, if paracetamol was a new drug. However cheap it was, it would be hard to convince purchasers to pay for something that did no more than doing nothing.

When you're in a hole, stop digging. Possibly one of the most sensible bits of advice for the situation we find ourselves in. Could it be that the key message is that the trials are lacking in sensitivity, and that while they are the best we have, they are just not good enough? Reviews like this may not change clinical practice, but they may change research practice, and that in turn should lead to us being better informed next time around.

And finally

And finally, this makes us think about how we should be wary of health economic analyses that fail to take account of all the evidence. If you sought cost comparisons between paracetamol, NSAIDs and coxibs in osteoarthritis, you would find at least one apparently useful paper [4].

It would tell you that paracetamol was quite a good buy, based on limited information. It may be, but if we can't tell the difference between paracetamol or nothing, how do we know? More pertinent, how do we know we are not doing the wrong thing?

References:

- 1 W Zhang et al. Does paracetamol (acetaminophen) reduce the pain of osteoarthritis?: a meta-analysis of randomised controlled trials. *Annals of the Rheumatic Diseases* 2004 63: 901-907.
- 2 A Wegman et al. Nonsteroidal anti-inflammatory drugs or acetaminophen for osteoarthritis of hip or knee? A systematic review of evidence and guidelines. *Journal of Rheumatology* 2004 31: 344-354.
- 3 C Miceli-Richard et al. Paracetamol in osteoarthritis of the knee. *Ann Rheum Dis* 2004 63: 923-930.
- 4 CC Kamath et al. The cost-effectiveness of acetaminophen, NSAIDs, and selective COX-2 inhibitors in the treatment of symptomatic knee osteoarthritis. *Value in Health* 2003 6: 144-157.

WHAT PATIENTS WANT

The informed patient is one who is aware of treatment options available to them, in terms of efficacy, harm, cost, and how much treatments may interfere with their daily activities. The informed patient has been a rarity, but is becoming less rare thanks to easier access to information through the Internet (though with misgivings about how reliable Internet information can be). Studies of treatment choices informed patients may make are very rare. One such [1] in knee osteoarthritis makes for interesting reading.

Study

This was a study at Yale in 100 consecutive patients living in the community with osteoarthritis of the knee. They had pain in one or both knees on most days of the month, had neither gout nor rheumatoid arthritis, and had not had a knee replacement.

In face-to-face interviews preference data on treatment choices and utilities were collected using conjoint analysis software that presented questions in a random order. Patients were given information about treatment efficacy, common adverse events, route and frequency of administration, onset of action and risk of ulcer for five treatments: nonselective NSAIDs, cox-2 inhibitors, opioid preparations, glucosamine and/or chondroitin (all oral), and capsaicin cream. The percentage of patients benefiting was set at 50% for all four oral medications, and 25% for topical capsaicin. Paracetamol was not included because most of these patients had already taken it.

Results

The average age of the 100 patients was 70 years, and 80% were women. Half had a current health status of fair or worse, a third had dyspepsia from nonselective NSAIDs, 22% had a previous ulcer and 5% had been ad-

Table 1: Utility values for different medication characteristics

Medication characteristics	Mean utility
One pill once a day	41
One pill four times a day	19
Cream three times a day	10
Onset 1-2 hours	50
Onset 1 week	34
Onset 2 weeks	20
Onset 4 weeks	2
100% benefit	56
75% benefit	39
50% benefit	18
25% benefit	1
Well tolerated	70
Nausea, diarrhoea, heartburn	15
Nausea, constipation, dizziness	10
No added risk of ulcer	72
1% added risk of ulcer	49
2% added risk of ulcer	24
8% added risk of ulcer	1

Table 2: Relative importance of different treatment characteristics

Characteristic	Relative importance (%)
Gastrointestinal ulcer	19
Common adverse events	19
Chance of benefit	15
Time to benefit	14
Route of administration	12

Table 3: Patient choices for different treatments, assuming a minimum copayment

Option	Base case	Ulcer risk decreased	Efficacy of anti-inflammatory drugs increased
Nonselective NSAID	0	0	0
Cox-2 inhibitors	23	24	36
Opioids	25	25	20
Glucosamine	18	18	15
Capsaicin	34	33	29

mitted to hospital for gastrointestinal bleeding. Most of them were using or had used nonselective NSAIDs, Cox-2 inhibitors, glucosamine and analgesic creams, but only a third had previously used opioid preparations. They were therefore experienced patients.

Patient values for medication characteristics are shown in Table 1. Utilities relating to cost or availability have been omitted because they are probably distinct for the USA.

High utility values were placed on once daily oral dosing, onset of action within a week, a higher level of patients benefiting, and low risk of common adverse events and low risk of ulcer.

The relative importance of these various characteristics is shown in Table 2. The distribution of these implies that patients considered multiple characteristics, but highest on the list were common adverse events and ulcer risk. Together these rated much higher than chance or timing of benefit, or route of administration.

All these things come together when patients are asked for their preference for treatment. Table 3 shows this for an example of where patients pay a monthly co-payment (\$10 per month for NSAIDs, cox-2 inhibitors, and opioid preparations; \$25 per month for glucosamine or capsaicin). Capsaicin was the most preferred, but none preferred NSAIDs. Decreasing the risk of ulcers made little difference, but increasing the efficacy of nonselective NSAIDs and cox-2 inhibitors from 50% to 75% of patients benefiting made cox-2 inhibitors the first choice.

Much the same results occurred when patients paid the full cost of their medicines. Patients with health status rated by them as fair or worse were less likely to choose capsaicin (26%) than those who felt well or very well (56%).

Comment

There is much to say about how informative this study is. That patients prefer rapid action, good effect, and few adverse events (common or rare) from a once a day medicine is predictable. That adverse events (common or rare) dominate over efficacy is predictable. Bandolier would not have predicted that topical capsaicin would be preferred over other choices, nor that traditional NSAIDs would be chosen by none. Where patient choice is meant to be increasingly important in healthcare, the difference between these results and most guidelines for treatment is stark. For most of those topical capsaicin would not get a look in, and NSAIDs would be preferred over Cox-2 inhibitors on grounds of acquisition costs.

It is worth questioning the assumptions patients were given over treatment scenarios rather than validity of the results. For topical capsaicin, for instance, the scenario may have been over-generous. A recent systematic review showed that there were only 368 patients in three randomised trials in musculoskeletal pain, and topical capsaicin was barely better than placebo [2].

For NSAIDs or Cox-2 inhibitors, the assumption that half patients benefit may be right, but the context is difficult. Even in clinical trials, 30% of patients with either treatment discontinue by about a year (Bandolier Internet review), and it is more with NSAIDs in clinical practice. There is a difference between short and long term benefit.

Missing from the analysis is how choices would be different if topical NSAIDs had been included. We know they work in knee arthritis, at least in short term trials. Longer term trials are coming that add to present evidence that topical

and oral NSAIDs have equal efficacy. They are safer by far, but not available in the USA, so were not included. Had they been, choices may well have been even more in favour of topical over oral drugs.

But these are quibbles. What we know is that what patients want may well be different from what we think they want. We could certainly do with more studies like this, and more information about what to do with this information when we have it.

References:

- 1 L Fraenkel et al. Treatment options in knee osteoarthritis. The patient's perspective. *Archives of Internal Medicine* 2004 164: 1299-1304.
- 2 L Mason et al. Systematic review of topical capsaicin for the treatment of chronic pain. *BMJ* 2004 328: 991-994.

KEEP TAKING THE MEDICINE

Bandolier has occasionally asked questions about compliance, or adherence, or concordance, because this is an important defining issue in healthcare, but one lacking some grip. It is partly because there are so many different definitions, and situations, that an over-arching summary is unlikely. Major differences may also crop up between clinical trials and clinical practice. In trials compliance may be good, but in practice adherence can be poor.

Bandolier 117 examined evidence both that there was better compliance with once or twice a day therapy, and that half of older people on statins had stopped taking them after five years. In clinical trials 90% of people remain on therapy, even in long duration studies.

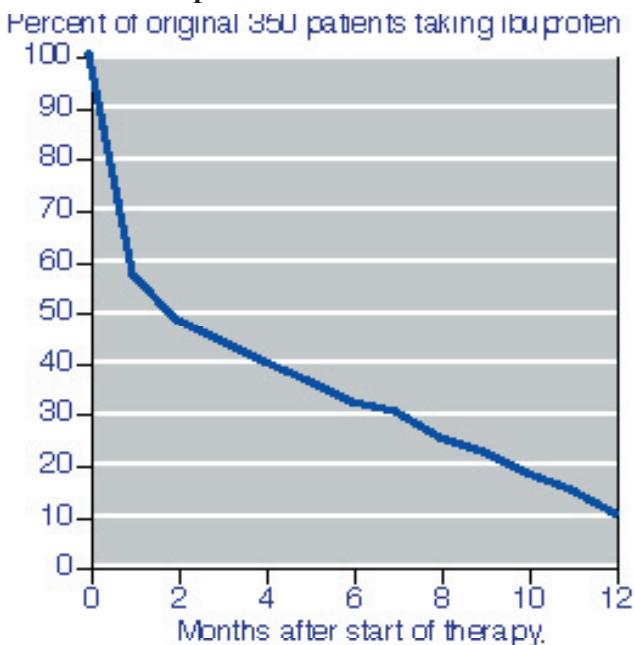
Bandolier 122 examined a paper showing that half the people in Scotland prescribed low dose aspirin didn't take it, and 38% of people with psychosis didn't take their medicines. The situation is not necessarily better elsewhere, so a few other examples might help us think it through. Three more examples, then, of how initial treatment is not maintained, for NSAIDs in arthritis, immunosuppressants after renal transplants, and contraception.

NSAID discontinuation in OA [1]

A retrospective cohort analysed 1,405 patients aged 45 years or more receiving a new prescription for one of four NSAIDs, who were followed for 12 months in Washington state [1]. Patients had a unique identifier, and manual and electronic databases ensured excellent identification of the last date drugs could have been used, based on prescriptions filled, quantity dispensed and instructions for use.

Within a month about 30% of people had discontinued, in three months it was half, and by the end of a year fewer than 20% of patients were still using the NSAID prescribed (Figure 1 for ibuprofen). In a meta-analysis of randomised trials [2] at 12 weeks the discontinuation rate was 26-40%, somewhat less than in clinical trials than in this retrospective analysis in clinical practice.

Figure 1: Discontinuations over 12 months in patients on NSAIDs

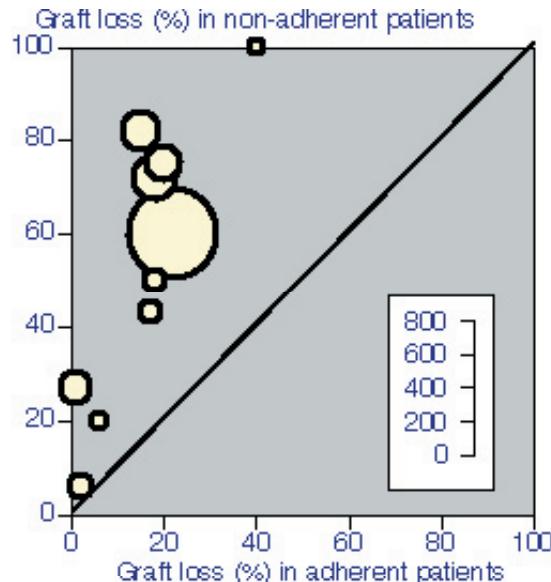


Immunosuppressants and renal transplant [3]

Even in patients who have had a kidney transplant, adherence to immunosuppressant treatment can be a problem. A systematic review [3] found 36 cohort, cross-sectional studies, and case series looking at the problem. There were various definitions of non-adherence, and different ways of measuring it, but essentially what was looked at was the quantity and frequency of missed medicines assessed by questionnaire or interview.

Cross-sectional studies found a median of 22% of patients were non-adherent, and the cohort studies 15%. Non-adherence here is different in type and degree from discontinuation in other studies, perhaps relating to occasional missed doses, or doses wrongly timed. Even so, there was a big impact relating non-adherence to graft loss (Figure 2).

Figure 2: Graft loss in patients adherent and nonadherent to immunosuppressives



The number of transplant failures in non-adherent patients was 125/289 (43%), compared with 296/1724 (17%) in those patients who were adherent. The relative risk was 3.5 (95% CI 2.9 to 4.2). For every four renal transplant patients who were non-adherent to immunosuppressive medicines rather than being adherent, one more suffered a graft loss (NNH 3.8; 95% CI 3.1 to 5).

Compliance and contraception [4]

Another example where we can see outcomes relating to lack of compliance is in contraception. An analysis of perfect and imperfect use of patch and oral contraceptives in the context of a clinical trial [4] had pregnancy as an outcome. Here perfect use was 21 consecutive days of hormonal contraceptive patch use with every patch changed at a 7-day interval, and perfect hormonal oral contraceptive use was 21 consecutive days of tablet ingestion. Anything else was considered imperfect dosing. Information was gathered from diary cards on an ongoing basis.

The number of pregnancies and cycles is shown in Table 1. Imperfect use of the contraceptive increased the pregnancy rate by about 5-10 fold, though there were few pregnancies. In a comparative study 11% of patch cycles were imperfect, somewhat less than the 21% of cycles using oral contraceptive. There was no effect of age. The lesson may be that longer-acting hormonal contraceptives give better contraceptive protection for women in real life.

Comment

Some patients do not keep taking the medicine. It may be understandable, because the medicine brings little benefit, and may do some harm. There may just seem not to be any benefit, as with a statin, where the results, after all, are statistical as much as personal. It will certainly be a bore, especially when there are lots of drugs to be taken at different times.

But there are costs. There are simple costs, like the tons of expensive medicines in medicine cabinets rather than people. There are costs because people do not benefit. A graft lost in a transplant patient is a tragedy.

The monetary value of non-adherence is huge. The cost of non-adherence in psychosis has been estimated to be £5,000 a year for a non-adherent patient [5]. A global figure for non-adherence costs in healthcare in the USA was a whopping US\$300 billion (sic). So this is a topic worth re-visiting when more evidence emerges.

Table 1: Effect of perfect and imperfect dosing on contraceptive effectiveness

Dosing and Treatment		Pregnancy	Cycles	Pregnancies per 1000 cycles
Perfect	Patch	3	4,558	0.7
	Oral	2	3,276	0.6
Imperfect	Patch	2	583	3.4
	Oral	5	858	5.8

References:

- D Scholes et al. Nonsteroidal anti-inflammatory drug discontinuation in patients with osteoarthritis. *Journal of Rheumatology* 1995 22: 708-712.
- JJ Deeks et al. Efficacy, tolerability and upper gastrointestinal safety of celecoxib for treatment of osteoarthritis and rheumatoid arthritis: systematic review of randomised controlled trials. *BMJ* 2002 325: 619-623.
- JA Butler et al. Frequency and impact of nonadherence to immunosuppressants after renal transplantation: a systematic review. *Transplantation* 2004 77: 769-789.
- DF Archer et al. The impact of improved compliance with a weekly contraceptive transdermal system (Ortho Evra®) in contraceptive efficacy. *Contraception* 2004 69: 189-195.
- M Knapp et al. Non-adherence to antipsychotic medication regimens: associations with resource use and costs. *British Journal Psychiatry*. 2004 184: 509-16.

DOSE REGIMENS AND COMPLIANCE

Bandolier 117 looked at a rather old (1984) review of dosing regimens and compliance, that concluded that once or twice a day regimens had better compliance (about 70%) than those in which patients had to take medicines three or four times a day. There were some problems with it, one of which was that it used pill count, interviews, and presence of drug in body fluids to assess compliance. A new systematic review of electronic monitors [1] comes to the same conclusion.

Electronic monitors use microprocessors to record the precise time that a dose is removed from the monitoring unit, and capture medication events. They record both the number of events, especially whether doses are missed, and whether doses are taken at the correct time.

Systematic review

The review used five electronic databases, including the Cochrane Library, to find reports of electronic monitoring use. Any device could be used, and medication compliance had to be reported. Studies for the years 1986 to 2000 were sought. Results were evaluated in terms both of the number of doses taken, and also the timing of doses to within 25% of the dosing interval. For 12 hour dosing, therefore, doses taken outside of plus or minus three hours were deemed inappropriate.

Results

The review found 76 studies with identifying dose taking or dose timing. Most (60) were bottle caps, 10 were metered dose inhalers, and two each pill boxes, blister cards, or eye drop dispensers. The majority of conditions were in cardiovascular and respiratory disease, though there was little difference in overall compliance between conditions, perhaps with the exception of respiratory disease where it was lower at about 50%.

Figure 1: Compliance - dose taking

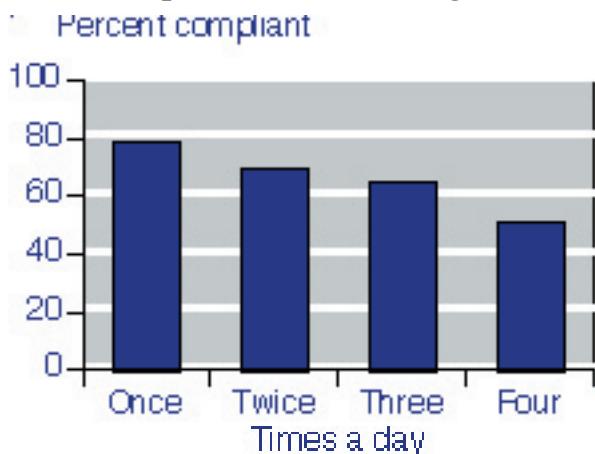


Figure 2: Compliance - dose timing

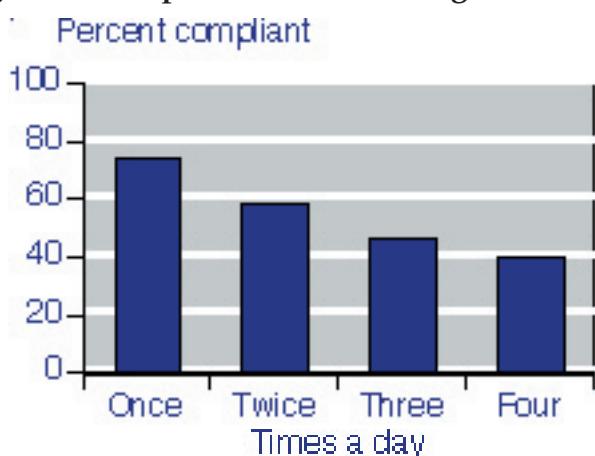


Table 1: Compliance in dose taking

Times a day	1984 review		New review	
	Range	Mean (SEM)	Range	Mean (SEM)
Once	42-93	73	35-97	79
Twice	50-94	70	38-90	69
Three times	18-89	52	40-91	65
Four times	11-66	42	33-81	51

Overall compliance for taking doses in 85 different regimens was 71%, with a range of 34% to 97% in individual studies. Once and twice a day dosing was higher than that for three and four times a day regimens (Figure 1). For dose timing in 14 reports, the proportion of medicines taken within the prescribed time was 58% for twice daily doing, and below 50% for three and four times a day dosing (Figure 2).

Comment

For dose taking compliance, the results here using electronic monitoring were substantially the same as those found in the older study using pill counts or patient interviews (Table 1). The results for timing were similar. Perhaps the lesson is to keep it simple, difficult though that is, particularly in older people with several conditions.

Reference:

- AJ Claxton et al. A systematic review of the association between dose regimens and medication compliance. *Clinical Therapeutics* 2001 34: 1296-1310.

IMPROVING COMPLIANCE

Most people do not take the medicines they are prescribed, and the obvious thing is to find ways of improving this. Two systematic reviews [1, 2] have found that interventions to improve compliance or adherence are pretty ineffective, and even those that are effective do not improve adherence by much. The problem of knowing what, if anything, to do is compounded by relative poverty of studies, in terms of their size and validity. A new review [3] concentrating on older patients in the community is a useful place to look at the problems.

Systematic review

Randomised trials of interventions aimed at improving medication adherence were sought in a variety of electronic databases. Results had to be on patients aged 60 years or older with a mean age of over 70 years who were living in the community. Total study size for all patients had to be above 50.

Results

Single generalised interventions were used in seven studies. Most were small, with numbers for intervention groups generally below 50 patients, and usually below 20 patients. In only one was the effect of the intervention measured at more than eight weeks. In one six-month study the numbers in intervention groups were about 20 patients. No single study was of a large enough size or long enough duration to be informative.

Three or more generalised or multifaceted interventions were used in eight studies. In five studies the duration was three months or longer and they were of reasonable size, with intervention or control group sizes of 50 or more in four of these five studies. In two of these there was a statistically significant improvement in an intervention group, but in neither was the magnitude of the benefit large.

Comment

In truth we know next to nothing about how to improve compliance with treatment in older patients. Yes, some studies show a significant effect, but not a big effect, and with little by way of utility to extrapolate elsewhere. The best we can say is that (possibly) multifaceted interventions involving a pharmacist help a bit.

References:

- Roter et al. Effectiveness of interventions to improve patient compliance: a meta-analysis. *Medical Care* 1998 36: 1138-1161.
- RB Haynes et al. Interventions for helping patients to follow prescriptions for medications (Cochrane Review). In: The Cochrane Library, 2002. Chichester, UK: John Wiley & Sons, Ltd.
- M van Eijken et al. Interventions to improve medication compliance in older patients living in the community. A systematic review of the literature. *Drugs Aging* 2003 20: 229-240.

BODY PIERCING AND RISK BEHAVIOUR IN ADOLESCENTS

Bandolier 109 examined some of the issues surrounding body piercing and body art. Body piercing was present in 42% of men and 60% of women undergraduates. Complications were reported in 17% of piercings, the most common being bacterial infections (9%), bleeding (4%) and local trauma (3%).

A new survey of piercing in younger adolescents [1] shows a lower incidence, and relates piercing to high-risk behaviour.

Survey

The survey was part of a US longitudinal study of adolescent health in which a random school-based sample was invited to complete two surveys at home in 1995 and 1996. The age range was 13-18 years, and was representative of US teenagers. Body piercing was related to sociodemographic factors, including family background and place of residence.

Results

There were 4,337 completed surveys. Piercing other than at the ear occurred in 4% overall, but was higher in girls (7.1%) than boys (1.5%), and was lower in 13-15 year olds (2.7%) than 16-18 year olds (5.6%). There were no differences according to ethnicity, residence or family circumstance.

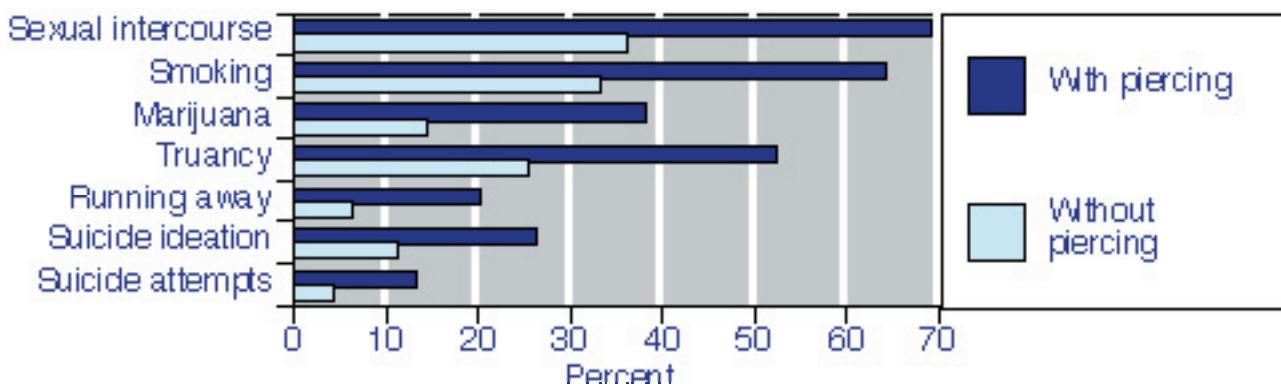
Body piercing was significantly related to a range of high-risk behaviours (Figure 1). These included sexual intercourse, substance abuse, truancy and running away from home, and, importantly, suicide ideation and attempts. Suicide ideation and attempts were found in 26% and 13% of adolescents with body piercing.

Medical problems with piercing

Two reviews [2, 3] have looked at serious medical problems with body piercing.

A systematic review [2] examines complications of nipple piercing. Ten cases were found, nine published since 1999. Seven were in women and three in men, with an age range of 15 to 60 years. The main comments were:

Figure 1: Body piercing and high risk behaviour in US adolescents



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- Interval between piercing and treatment was 2-52 weeks.
- Duration of symptoms was one week to several months.
- Nine patients had antibiotics.
- Seven patients also needed an operation.
- Major complications included endocarditis, heart valve operation, prosthesis infection, metal foreign body, one reoperation because of infection, psychological stress from incorrect primary diagnosis of breast cancer in two cases.

A second review [3] examines eight published case reports of infective endocarditis associated with piercing of tongue (3), ear (2), and nipple, nose and navel. In five of these surgery was recommended, mainly for removal of an aortic valve. Two of these five did not return for treatment.

Comment

Body piercing is risky in itself, as well as being a marker for higher risk behaviours. The US adolescent study has the demerit of possibly being behind the times, as over the nine years since it started collecting data piercing has become much more common.

References:

- 1 TA Roberts et al. Body piercing and high-risk behaviour in adolescents. *Journal of Adolescent Health* 2004 34: 224-229.
- 2 VR Jacobs et al. Mastitis nonpuerperalis after nipple piercing: time to act. *International Journal of Fertility* 2003 48: 226-231.
- 3 BC Millar, JE Moore. Antibiotic prophylaxis, body piercing and infective endocarditis. *Journal of Antimicrobial Chemotherapy* 2004 53: 123-126.